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Combined exercise training modulates extracellular vesicle–associated microRNAs and tumor transcriptomics in breast cancer patients during a pre-treatment window-of-opportunity

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Background: Physical exercise training can reduce breast cancer progression. It has been proposed that exercise may directly influence tumor transcriptional activity through antitumoral intercellular communication, mediated by extracellular vesicles (EVs) and their microRNA (miRNA)-associated cargo transiently released after repeated exercise bouts. **Purpose:** To investigate the effects of combined resistance and aerobic training (CT) on EV-associated miRNAs and breast tumor transcriptomics in breast cancer patients. **Methods:** Breast cancer patients enrolled in a window-of-opportunity clinical trial performed a CT program prior to oncological treatment. Blood was collected before and immediately after the first and last CT sessions (acute responses in untrained/trained states). Tumor biopsies were obtained before and after CT. Tumor RNA-sequencing was conducted on paired biopsies from a subset of three patients. Plasma samples were pooled by timepoint/training state for EV-miRNA profiling. EVs were isolated by size-exclusion chromatography. EV-associated miRNAs were profiled by small RNA sequencing and miRNAs were crossed with inversely regulated tumor genes. **Results:** A total of 416 EV-miRNAs were identified. Across conditions, several upregulated EV-miRNAs were classified as tumor-suppressor miRNAs (TSmiRs), whereas multiple downregulated miRNAs corresponded to known oncomiRs in breast cancer. hsa-miR-206, a skeletal muscle–enriched TSmiR, was consistently increased acutely in both untrained/trained states and chronically after CT. Members of the let-7-miRNA family, recognized for tumor-suppressive activity, also responded acutely to CT. Notably, hsa-miR-26a-5p (TSmiR) was exclusively and abundantly detected post-exercise. Tumor RNA-seq revealed no statistically significant gene-level changes; however, pathway analyses showed enrichment of metabolic pathways (PPAR, AMPK/cAMP signaling, cholesterol metabolism) among upregulated genes and enrichment of breast cancer–related and cytokine–cytokine receptor interaction pathways among downregulated genes. **Conclusion:** CT performed before oncological treatment induces acute/chronic remodeling of EV-associated miRNA expression favoring tumor-suppressive regulatory activity. Exploratory tumor transcriptomic analyses suggest metabolic reprogramming with reduced inflammatory/proliferative signaling, consistent with partial attenuation of a Warburg-like metabolic phenotype.

Keywords

Breast Cancer; Physical Exercise; Extracellular Vesicles; miRNAs

Conflict of Interest & Ethical Approval

yes

Abstract submitters declaration

yes

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